

Coeliac Disease with Diabetes: More than through chance alone

By Dr Albert Hsieh and Professor Stephen Twigg*

Coeliac disease, also known as gluten-sensitive enteropathy or nontropical sprue, was classified by World Health Organisation as a disease of digestive system causing intestinal malabsorption¹.

The prevalence of coeliac disease in the general community is reported as about 1 in 100 with higher prevalence in those who have family history of coeliac disease²⁻⁶. The condition is defined by the presence of circulatory antibodies such as anti-endomysial antibody or tissue transglutaminase antibody with small bowel biopsy showing villous atrophy that regresses with withdrawal of gluten in the diet. However, the development and clinical manifestations of the coeliac disease shows the condition is in fact an organ specific autoimmune disorder which is associated with multiple autoimmune diseases such as type 1 diabetes mellitus⁷⁻¹⁰, thyroid disease¹¹⁻¹², and liver disease¹³.

This article will briefly introduce diabetes mellitus, treatment and complications associated with diabetes, and relationship between diabetes mellitus and coeliac disease.

What is diabetes mellitus?

Diabetes mellitus is a metabolic condition where a person develops high blood glucose outside the physiological range, either as a result of insufficient insulin production or decreased insulin sensitivity in the body. The condition commonly produces classic symptoms of polydipsia (increased thirst), polyuria (frequent urination), increased fatigue, or weight loss. Diabetes is formally diagnosed based on one of the diagnostic criteria¹⁴ (Table 1). There are two main types of diabetes mellitus: type 1 and type 2 diabetes mellitus. A less common type of diabetes mellitus, known as latent autoimmune diabetes of the adult, is also presented here as it is associated with coeliac disease.

Type 1 Diabetes Mellitus

Approximately 14% of people with diabetes in Australia are reported to have the autoimmune form of

diabetes known as type 1 diabetes, and coeliac disease is closely associated with Type 1 diabetes¹⁵. Type 1 diabetes develops when the immune system destroys the β cells in the pancreas, which are responsible for producing the hormone insulin that regulates blood glucose. The autoimmune nature of the condition could be confirmed with the presence of antibody in the blood (Table 2). Type 1 diabetes usually develops in children and adults before the age of 30, although the disease can develop at any age. Treatment would involve insulin therapy either in the form of multiple daily injections or pump therapy, together with calculated carbohydrate intake and frequent glucose monitoring. As blood glucose fluctuates from day to day, we now use glycosylated haemoglobin percentage, known as HbA1c, to monitor glucose control over a three-month period.

Type 1 diabetes complications

Tight glucose control is very important in type 1 diabetic patients as poor blood glucose control can have both short term and long term complications. In the short term, insufficient insulin therapy could lead to high blood glucose in the circulation (hyperglycaemia) while the body could not utilise the glucose as energy. As the body falsely perceives that it is in a starved state, it would use fat and protein as alternative energy sources. This would quickly result in acid in the blood known as diabetic ketoacidosis and in severe cases, death could ensue if left untreated. In reality, many people with new onset type 1 diabetes are diagnosed initially as a result of diabetic ketoacidosis. People with type 1 diabetes are educated regarding how to avoid diabetic ketoacidosis and how to manage it when they suspect they are at risk of developing the complication.

Table 1. Diagnostic Criteria for Diabetes Mellitus

1. Glycosylated Haemoglobin A1C percentage (HbA1c) of greater or equal to 6.5 OR
2. Fasting plasma glucose level of greater or equal to 7.0mmol/L OR
3. During an oral glucose tolerance test, the two hour plasma glucose level of more than 11.1mmol/L OR
4. A random plasma glucose level of greater or equal to 11.1 mmol/L in a patient with classic symptoms of hyperglycaemia

Table 2. Antibodies that occur in diabetes or in coeliac disease

- A. Antibody testing associated with diagnosis of a case of diabetes as an autoimmune based diabetes (type 1 diabetes or LADA):
 - Insulin antibody (IA)
 - Islet cell antibody (ICA)
 - Glutamic acid decarboxylase antibody (GADA)
 - Insulinoma-associated protein 2 antibody (IA-2)
 - Zinc transporter antibody (ZnT8)
- B. Antibody testing associated with coeliac disease and its screening:
 - Anti-tissue transglutaminase Antibody
 - Anti-endomysial antibody
 - Anti-gliadin antibody

On the opposite end of hyperglycaemia, insufficient carbohydrate intake or excessive insulin therapy could lead to hypoglycaemia (low blood sugar). The most acute effect is neurogenic symptoms, when low blood glucose affects brain function, causing symptoms such as tremor, palpitations, anxiety, sweating. In the severe end of the spectrum, hypoglycaemia could cause neuroglycopenic symptoms, for instance, confusion, behavioural changes, seizures or coma if carbohydrate is not supplemented quickly. If available, glucagon injection should be deployed followed by carbohydrate supplementation during the early recovery phase.

In practice most people with type 1 diabetes are able to avoid frequent severe hypo- or severe hyperglycaemia. It is the longer term complications of diabetes that progressively become a concern. In the long run in type 1 diabetes a number of complications could happen as a result of chronic hyperglycemia: diabetic retinopathy (eye disease), neuropathy (nerve damage) and nephropathy (kidney disease). The triad is known as microvascular (small vessel) complications of the diabetes. These are monitored through regular ophthalmology review, nerve ending test and measuring kidney function with urinary protein level. The other spectrum of complications are related to large vessels in the body, otherwise known as macrovascular complications, such as ischaemic heart disease that could cause angina or heart attack, stroke or peripheral vascular diseases. These complications can be minimised in amount and severity if long term blood glucose control (HbA1c) is kept well controlled with intensive diabetes management.

Type 2 Diabetes Mellitus

In Australia, 83% of diabetic patients are reported to have type 2 diabetes¹⁵. Although type 2 diabetic patients still produce insulin in their bodies, the high blood glucose is either due to "insulin resistance", where the body is unable to utilise the insulin properly and/or there is relative deficiency in insulin secretion. Type 2 diabetes mellitus generally develops in middle age or older patients. In the recent years, however, we are seeing more and

more patients being diagnosed in early adulthood or late adolescence. The risk factors include obesity, family history of diabetes, history of diabetes during pregnancy (gestational diabetes mellitus), physical inactivity, and certain race/ethnicity: for instance, Indigenous Australians are 3 to 4 times more likely to develop diabetes than non indigenous population¹⁵. Although there is no association between type 2 diabetes and coeliac disease, it is important to remember that patients with coeliac disease could still develop type 2 diabetes later in life if they have multiple risk factors.

Latent autoimmune diabetes of adulthood (LADA) / Autoimmune type of diabetes not requiring insulin at diagnosis.

A small subset of adult onset diabetes, known as latent autoimmune diabetes of adulthood (abbreviated as LADA), carries similar risk for development of coeliac disease as type 1 diabetes mellitus¹⁹. Although this condition initially does not appear to require insulin therapy and is clinically similar to type 2 diabetes mellitus, the majority of people with this condition will become dependent on insulin therapy much faster than the person with typical type 2 diabetes. As a result of the similar genetic susceptibility as type 1 diabetes sufferers¹⁹, people with LADA would likely also carry similar risk for development of coeliac disease in life.

Association between coeliac disease and type I diabetes

Type I Diabetes and Coeliac Disease

Approximately 4-10% of people with type 1 diabetes have been reported to have coeliac disease^{10, 20-28}. The diagnosis is established by antibody testing with confirmation on small bowel biopsy. Despite the positive biopsy results, most of the patients with coeliac disease do not have the classic symptoms of abdominal pain, foul-smelling and/or floating diarrhoea, or weight loss. In fact, they either have mild and non specific symptoms such as fatigue, mildly elevated liver function tests, or no symptoms at all⁴.

Genetic susceptibility

Type 1 diabetes and coeliac disease share multiple susceptibility genes both inside the immune regulatory parts of the genome, known as human leukocyte antigen (HLA) genes, as well as outside the immune regulatory parts of the genome^{8, 29-32}. This strongly suggests these two conditions have common pathological processes causing tissue damages from autoimmunity. However, a causal relationship between coeliac disease and diabetes mellitus is not established.

Screening

As the two conditions carry life changing implications to those diagnosed with the diseases, when to screen for coeliac disease in people with type 1 diabetes becomes important. There is debate regarding the timing and sequence of onset of diabetes mellitus and development of coeliac disease antibody. Earlier studies suggest that coeliac disease antibody develops later than type 1 diabetes-associated antibody; however, the latest study demonstrated that coeliac disease associated antibody develops mostly at a younger age or the same age as the development of diabetes antibody^{21, 33-35}.

Due to the strong association of coeliac disease with type 1 diabetes, the American Diabetes Association recommends that "... children with type 1 diabetes should be screened for coeliac disease by measuring tissue transglutaminase or anti-endomysial antibodies with documentation of normal serum IgA levels, soon after the diagnosis of diabetes". IgA (one type of immunoglobulin) can be deficient in a coeliac disease sufferer and so could result in false negative test results. The guideline also recommends that testing should be repeated, and some Australian guidelines in type 1 diabetes developed from research including locally based studies, recommend rescreening for coeliac disease each ~2 to 3 years in children and adolescents³⁶. In addition, if symptoms such as growth failure or gastrointestinal symptoms occur then antibody tests should be undertaken in order to diagnose coeliac disease in a timely manner^{14, 25, 28, 37-38}.

Implications of coeliac disease in type 1 diabetes management

Coeliac disease can potentially interfere with glucose metabolism as it causes malabsorptive (lack of absorption) disease secondary to damage of the gut mucosa. However, there is no clear consensus whether coeliac disease affects blood glucose control or insulin requirement in people with type 1 diabetic patients. Some studies suggest that coeliac disease is associated with increased risk of hypoglycaemia and the introduction of a gluten free diet appears to reduce the frequency of hypoglycaemic events³⁹⁻⁴². However, there is conflicting evidence showing that no statistically significant effect of a gluten free diet in growth, diabetes control or nutrient intake between people with type 1 diabetes who have, or do not have, coeliac disease^{10, 43-44}.

Despite the conflicting evidence, it is certain that the only definitive treatment for coeliac disease is a strict gluten free diet. Similarly, all people with type 1 diabetes should eat a well-balanced diet with proportioned carbohydrate intake. As gluten is contained in many foods, particularly in products made from wheat, barley, rye, and oats, it is important that people with type 1 diabetes who have newly diagnosed coeliac disease discuss their dietary choices with a qualified dietitian, while closely monitoring their insulin requirement and regularly checking their blood glucose level to avoid hypoglycaemia episodes. Individual patients should also have a 'hypoglycaemia action plan' with a handy 'hypo pack' to apply prompt treatment if they experience a hypoglycaemic episode. Should there be an episode of hypoglycaemia while no gluten free source of carbohydrate is available, the patient should consume gluten containing carbohydrate without hesitation as the immediate danger associated with uncorrected hypoglycaemia is significant.

Lastly, low bone density (osteoporosis) can occur in people with coeliac disease and in those with type 1 diabetes⁴⁵, and it is prudent to assess bone mineral density in adults who have both of these conditions. Calcium intake and vitamin D levels should also be optimised especially if the bone density is low.

Summary Points in Snapshot:

- Type 1 diabetes increases the risk of a person developing coeliac disease by about 10 fold. From another perspective, up to 10% of people who have type 1 diabetes will develop coeliac disease.
- Coeliac disease may occur before or after the diagnosis of type 1 diabetes, sometimes many years after insulin treatment has been started for the diabetes.
- People who have the 'slower onset' diabetes condition known as latent autoimmune diabetes of adulthood (LADA) may have a similar risk of developing coeliac disease as people with type 1 diabetes.
- In people with type 1 diabetes, most cases of coeliac disease these days will be diagnosed by screening blood tests rather than through symptoms or clinical signs of the disease. It is recommended that screening for coeliac disease be undertaken by appropriate antibody blood tests at diabetes diagnosis then at intervals of ~2 years thereafter. In those with positive screening results for coeliac disease, an upper gastro-intestinal endoscopy with small bowel biopsy and pathology assessment of the sampled tissue is required to make the diagnosis of coeliac disease.
- Gluten exclusion treatment for coeliac disease in people with type 1 diabetes may or may not help control of blood glucose and the responses between different individuals can be quite variable. Irrespective of the effects on blood glucose, once it is definitively diagnosed, coeliac disease should be treated in people with type 1 diabetes to help prevent coeliac disease complications long term.
- Low bone density (osteoporosis) can occur in people with coeliac disease and in those with type 1 diabetes and bone density could be assessed in adults with both conditions.
- With ongoing support in their self-care despite the demands in treatment, a person who has both type 1 diabetes and coeliac disease can lead a full and high quality life, free from major tissue and organ complications.

Conclusion

Coeliac disease and type 1 diabetes mellitus are both life changing conditions and there is no curative treatment available for type 1 diabetes mellitus. However, through balanced lifestyle and appropriate control, individuals can lead a healthy and productive life with appropriate support. For further questions regarding diabetes and coeliac disease, it is suggested that the reader refer to the booklet "living with diabetes & coeliac disease" prepared by the Coeliac Society of Australia and State and territory Diabetes Organisations or consult the web pages <http://www.coeliacsociety.com.au/con-type1.html> for further information.

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References:

Members wishing to receive a copy of the references, please email: info@coeliacsociety.com.au or send a stamped, self-addressed envelope to:

References, March 2011
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